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INVITED COMMENTARY

Genetic Confounds in the Study of Sexual Orientation: Comment on Roberts, Glymour, and Koenen (2014)

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Roberts, Glymour, and Koenen (2013) presented evidence that childhood maltreatment is related to adult homosexuality, using an instrumental variables regression analysis. Briefly, several instrumental variables—presence of a stepparent, poverty, parental alcohol abuse, and parental mental illness—were related to adult homosexuality, but these relations were statistically mediated by childhood maltreatment. Roberts et al. concluded that childhood maltreatment causes adult homosexuality.

We criticized the statistical approach of Roberts et al. (2013), arguing that the assumptions of both instrumental variables regression and mediation analysis were almost certainly violated (Bailey & Bailey, 2013). The instruments—stepparent presence, poverty, parental alcohol abuse, and parental mental illness—are complex in their causes and effects, and might be correlated with adult sexual orientation, through a multitude of complex pathways that do not require adult sexual orientation to be caused by the instruments via childhood maltreatment. The study falls far short of being a "natural experiment," on which the instrumental variables regression approach is designed to capitalize, despite Roberts et al.'s characterization of their study as such. If an unmeasured third variable can cause both the instruments and outcome, the results from instrumental variables regression and mediation analyses cannot be taken as evidence for the causal pathways tested in these models.

We proposed that the findings from Roberts et al. (2013) were equally consistent with an alternative causal explanation of adult sexual orientation, where genes that influence an individual's sexual orientation also influence an individual's personality. Both neuroticism (Zietsch, Verweij, Bailey, Wright, & Martin, 2011) and depression (Zietsch et al., 2012) have been found to correlate at the genetic level with adult sexual orientation. Therefore, parents with these genes may be more likely to divorce (resulting in stepparent presence), live in poverty, abuse alcohol, be diagnosed with mental illness, and to have children who are maltreated. Under this model, Roberts et al.'s instrumental variables regression and mediation analyses would yield apparent evidence for an influence of childhood maltreatment on adult sexual orientation, even though maltreatment does not cause adult sexual orientation.

Roberts, Glymour, and Koenen (2014) criticized our reply, stating that "no genetic research supports [the] possibility" that genes associated with sexual orientation may also be related to parental relationship instability, mental illness, alcohol use, and poverty. Further, they claim that, for the hypothesis we proposed to account for their findings, homosexuality and neuroticism must both be caused by an allele of very large effect (accounting for 14 % of the variance in mother's neuroticism and 15 % of the variance in child's sexual orientation). Roberts et al. asserted that these effects "are stronger, by an order of magnitude, than any established genetic determinant for any mental health or complex behavioral outcome."

If we understand "established genetic determinant" as a single gene, then we agree with Roberts et al. (2014). To date, there have been no replicable findings of genes with effects of this magnitude (i.e., 14 % of the variance in neuroticism and 15 % of the variance in sexual orientation). However, our argument does not rely on the assumption that the genetic correlation is due to a

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single gene and the assertion that it does indicates a major misunderstanding.

The Missing Heritability Problem

As Roberts et al. (2014) noted, the associations between specific genes and psychiatric disorders are surprisingly low. For example, Roberts et al. noted that common alleles can only account for a small amount of the variance in schizophrenia (Purcell et al., 2009). A more recent study estimated that approximately one quarter of the variance in schizophrenia could be accounted for by common variants (Lee et al., 2012). Regardless, neither of these studies indicates that the majority of the variance in schizophrenia can be attributed to environmental factors. On the contrary, Purcell et al. noted that estimates of the heritability of schizophrenia have approached 80 %. The same pattern holds in the cases of personality—no variant of major effect has been found to be related to personality traits (de Moor et al., 2010), yet approximately 50 % of the variance in personality traits is associated with genetic variation (Bouchard & Loehlin, 2001)—and sexual orientation—no variant of major effect has been well established for male sexual orientation (e.g., DuPree, Mustanski, Bocklandt, Nievergelt, & Hamer, 2004), yet twin studies have generally found evidence for moderate heritability (e.g., Bailey, Dunne, & Martin, 2000; Kendler, Thornton, Gilman, & Kessler, 2000). The large discrepancy between the proportion of variance in psychiatric disorders (and other traits, such as height, intelligence, sexual orientation, and personality traits) associated with individual common genetic variants and estimates of the heritability of these disorders is known as the "missing heritability" (Manolio et al., 2009). One explanation for the missing heritability problem that has received empirical support (Yang et al., 2010) is that traits are caused by a large number of variants, each with a very small average effect. This would account for the low number of identified replicable variants associated with psychiatric disorders and personality in genome-wide association studies.

Some methodological approaches, such as twin and adoption studies, bypass the missing heritability problem by estimating genetic factors comprised of all unmeasured genetic effects that account for variance in, or covariance between, phenotypes, regardless of proportion of variation/covariation accounted for by any specific gene. Our hypothesis that common genetic factors influence both the instruments and sexual orientation is based on evidence from twin studies.

Latent Genetic Correlation

If sexual orientation and personality are influenced by a large number of genes, perhaps some affect both personality and sexual orientation. But if several genes affect both, is it likely that they would affect sexual orientation and personality traits consistently in the same direction? Evidence from twin studies suggests that it is indeed likely. Many massively polygenic traits show correlations at the genetic level, such as height and intelligence (Keller et al., 2013). Indeed, neuroticism (Zietsch et al., 2011) and depression (Zietsch et al., 2012) correlate at the genetic level with adult sexual orientation.

The Genetic Correlation Explanation Revisited

When the misunderstanding that genetic correlations must be caused by a single allele is replaced with the correct understanding that many alleles of minor effect can cause even very large genetic correlations, our hypothesis fits well with the assumptions that Roberts et al. (2014) claim our hypothesis necessitates. For example, Zietsch et al. (2012) observed a genetic correlation of .42 between depression and sexual orientation. The heritability of depression was .44 and the heritability of sexual orientation was .31. Using the Cholesky approach (Neale & Cardon, 1992), we estimated that genetic factors associated with depression predicted 44 % of the variance in depression and 5.5 % of the variance in sexual orientation.[1] If other instruments are correlated at the genetic level with sexual orientation (below, we argue that this is quite plausible), genetic factors associated with the instruments could reasonably account for 15 % of the variance in sexual orientation (and for well over 14 % of the relevant personality traits).

Finally, we will revisit Roberts et al.'s (2014) claim that genetic research does not support the possibility that the parents of homosexual children might be at higher genetic risk for relationship instability, mental illness, alcohol use, and poverty. Neuroticism is correlated at the genetic level with divorce risk (Jocklin, McGue, & Lykken, 1996), anxiety and depression (Jardine, Martin, Henderson, & Rao, 1984), and alcohol use disorders (Littlefield et al., 2011). We are not aware of a study that investigated the genetic correlation between neuroticism and poverty, but socioeconomic status is moderately heritable (Rowe, Vesterdal, & Rodgers, 1999) and financial security is negatively correlated with neuroticism (Roberts, Caspi, & Moffitt, 2003).

[1] From Zietsch et al. (2012), the variance in sexual orientation is attributed to genetic factors shared with depression (factor loading of $.24^2$), genetic factors unshared with sexual orientation ($.56^2$), common environmental factors (i.e., environmental factors that make twins similar; $.45^2$), and unique environmental factors (i.e., environmental factors that make twins different, $.69^2$). Therefore, the proportion of variance attributed to genetic factors shared with depression is 5.5 %, the factor loading from genetic factors for depression ($.24^2$) divided by the total variance in sexual orientation ($.24^2 + .56^2 + .45^2 + .69^2$). We have confirmed this estimate with Zietsch.

To our knowledge, studies measuring genetic correlations between sexual orientation and these variables are limited to Zietsch et al.'s studies of sexual orientation and neuroticism, psychoticism, and depression. However, given the genetic correlation between sexual orientation and neuroticism, the moderate heritability of sexual orientation, personality traits, and all of the instruments, and the phenotypic correlations between sexual orientation and substance use disorders (Talley, Sher, & Littlefield, 2010), psychopathology[2] (Fergusson, Horwood, Ridder, & Beautrais, 2005; Gilman et al., 2001), and poverty (Lee Badgett, Durso, & Schneebaum, 2013), we think that genetic correlations between sexual orientation and these variables are quite plausible as well.

In summary, a wide body of research from the field of behavior genetics suggests that correlations between parents' and children's traits and behaviors are often (or even usually) attributable to processes other than direct effects of parenting on child outcomes. Of course, environmental factors play a major role in children's development. However, any study that treats children's biological parents as conditions in a "natural experiment" ignores a major potential confound: shared genes between parents and their children.

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[2] We echo the sentiment of Zietsch et al. (2012): we do not intend to pathologize homosexuality by pointing out its shared etiology with neuroticism and psychopathology. Less socially sensitive topics, such as non-right-handedness are also associated with psychopathology, but we do not view them as pathological either.

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